

Evaluation of intermolecular interactions of self-etch dentin adhesive primer molecules with type 1 collagen: Computer modeling and in vitro binding analysis

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Abstract

The objective of this investigation was to study adhesion of self-etch primer systems to dentin by computer-modeled docking simulations and in vitro binding assay methods. Computer modeling employed analysis of docking simulations of a self-etch primer molecule 10-methacryloxydecamethylene phosphoric acid (MDP) and its calcium salt (MDPCa) as ligands. Typical type 1 collagen segments were selected as targets to reflect potential differences in the amino acid residues in dentinal type 1 collagen triple helix motif. The binding assay involved immunochemical analysis of the modification of anti-collagen binding to collagen by prior exposure of the demineralized dentin to MDP. The estimated mean docking energy values ranged between -4.5 and -8.9 kcal mol⁻¹. The results revealed significant differences in the docking energy estimates as a function of ligand and target structures ($p < 0.01$). Van der Waals and electrostatic contributions were also significantly influenced by ligand selection and collagen structure. Both MDP and MDPCa appear to be important in the overall interactions. Binding assay studies also lend evidence of collagen–ligand intermolecular interactions. It is suggested that the ability of self-etch dentin primer systems to bond effectively to dentin is not limited to the interaction of the primer with the hydroxyapatite of dentin, but also due to the ability to prime dentin efficiently through intermolecular interactions between the primer and its calcium salt with the collagen matrix. Virtual screening methods may be very valuable to select primer molecules for dentin bonding. © 2007 Published by Elsevier Ltd on behalf of Acta Materialia Inc.

Keywords: Collagen; Primer ligand; Docking; Interaction energy; Immunochemical binding

1. Introduction

The bonding of restorations to tooth, especially dentin, has been a critical issue in dentistry for many years. Current bonding techniques to dentin use priming and adhesive resin monomers to establish a transitional tissue–resin hybrid layer, and many investigations have addressed dentin bonding issues during the last few decades [1–17]. However, complex interfacial events, which occur during dentin bonding, have not been fully understood. The formation of a hybrid layer at the dentin–restoration

interface has nevertheless been recognized as the seminal event that causes more stable integration between the dentin substrate, the primer, the adhesive resin and the restoration [1,2]. A very important question that has not been fully answered so far is whether there are intermolecular adhesive interactions between the primer and tissue phases within the hybrid layer.

Two distinct approaches have been used to create the hybrid layer. In the first approach, the tissue is etched with an acidic solution or gel, thoroughly rinsed and primed in a moist environment (wet bond technique). Adhesive monomers are subsequently applied in a separate step to ensure copolymerization of the bonding layer with the composite restoration. In the second approach, the tissue is treated

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with a self-etching primer followed by adhesive monomer or a self-etch primer–adhesive resin formulation in a single step.

In the case of the etch, prime and wet bond approach, demineralization and rinsing remove the mineral phase from both the smear layer at the tissue surface and the underlying superficial layer of intact dentin tissue. In addition, all dislodged type 1 collagen fibrils in the smear layer are also removed. This leaves mainly a type 1 collagen-rich matrix at the tissue surface as the bonding substrate. In the wet bonding technique, the fibrils of type 1 collagen are water-bridged (or hydrogen bonded) to a “swollen” state, providing significant open or vacant interfibrillar/intrafibrillar space for primer permeation [1,2]. Such permeation may bring the primer molecules to close proximity to the substrate at the atomic and molecular levels, causing potential adhesive interactions [3,4]. Polymerization of the primer and adhesive monomers ensures cohesive strength within the restored structure. On the other hand, the interaction of self-etch primers with dentin does not remove the mineral phase or smear layer from the dentin surface. Rather, the primer permeates into the tissue surface through the porous smear layer and the superficial layer of dentin. This helps to facilitate the primer to interact with both the hydroxyapatite mineral phase as well as the type 1 collagen phase of the tissue structure, both in the smear layer and the underlying region of intact dentin penetrated by the primer.

The interaction of the hydroxyapatite phase to self-etching primers, such as MDP and Phenyl P, leading to the formation of their calcium salts, were recently analyzed through analytical techniques [5–7]. The permeation of the primer molecules into the dentinal structure also bring them in close proximity to type 1 collagen matrix phase causing potential van der Waals, electrostatic and hydrogen bonding interactions [3,4]. In addition, the formation of the calcium salt of the primer through its interaction with hydroxyapatite may also cause additional secondary interactions of this salt with type 1 collagen. However, there has been no reported study to evaluate the potential interaction between type 1 collagen and self-etch primers, or their calcium salts.

Fourier transform infrared (FTIR) and other analytical techniques have generally been reported to be not very responsive to the low energy interactions between the organic matrix of dentin and adhesive primers and their salts, but ^{13}C nuclear magnetic resonance (NMR) studies by Nishiyama et al. have indicated broadening of carbonyl peaks, indicating potential interactions involving type 1 collagen and acidic primer monomers [8,9]. Computer simulations using molecular modeling are, however, powerful tools to characterize protein–ligand interactions [3,4]. The integrity and cohesion within the hybrid layer may be strongly influenced not only by cohesive forces within the different phases constituting the hybrid layer, but also by adhesive forces between different phases in the hybrid structure, especially the atomic or molecular level forces.

It is therefore important to estimate the energy of interactions between the type 1 collagen matrix phase and the primer and its calcium salt, since these forces may significantly contribute to the integrity and durability of the hybrid layer in self-etch bonding systems. The individual α -chains of type 1 collagen structure are primarily made up of (Gly–X–Y) amino acid triplets, where X and Y may often be proline and hydroxyproline, respectively. But other residues, such as alanine, glutamic acid and lysine, have also been demonstrated to be present in the dentinal collagen structure [18], and in some cases such substituted residues may alter the local charge distributions or spatial relationships of atoms in the collagen matrix [19,20]. For this reason, significant effort has been focused on developing computational models of homologues of collagen, and some of these have been deposited in international databases such as RSCB PDB [21].

The presence of acidic (e.g. glutamic acid) and basic (e.g. lysine) residues, as well as size differences of residues in the repeat structure of collagen, may significantly modify the type 1 collagen matrix as a bonding substrate. In this study, we report a computational analysis of the van der Waals and electrostatic contribution to the total interaction energy of important homologues of type 1 collagen with a phosphoric acid-based ligand, 10-methacryloyloxydecamethylene phosphoric acid (MDP; widely used as a self-etch dentin adhesive primer), and its calcium salt (MDPCa). The objective was to assess adhesive interactions between representative type 1 collagen structural homologues in dentin and MDP as well as in its calcium salt. The null hypotheses tested were the following:

1. There is no significant difference in the collagen interaction with the primer and its calcium salt.
2. There is no significant difference in the collagen primer interactions due to differences in the primary structure of amino acid residues of collagen triple helix.

We also evaluated the interaction of MDP with demineralized surfaces of dentin by immunochemical analysis of anti-collagen binding to collagen before and after ligand treatment.

2. Materials and methods

Although different models, such as the Smith collagen microfibril twisted equilateral pentagonal model [22] and Hulmes and Miller quasi-hexagonal model [23], have been proposed as collagen molecular packing arrangements, at the molecular level, the triple helix motif is recognized at the present time as the basis of both packing arrangements [24]. Three type 1 collagen molecular models based on the triple helix motif were studied as docking target structures in this investigation. The triple helix models were simulated coil–coil structures of three α -chains with 30 residues each for a total of 90 residues in the collagen model. The first model used was RCSB PDB file 1CGD, with the residue

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